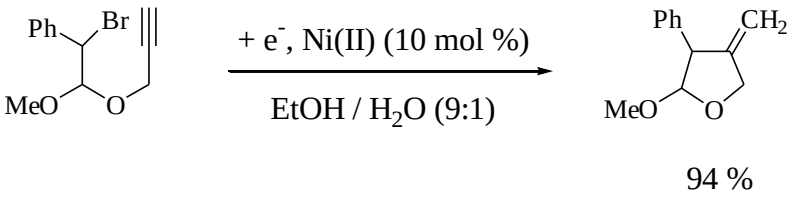
Graphical abstract

INDIRECT ELECTROCHEMICAL CYCLIZATION OF BROMOALKOXYLATED DERIVATIVES MEDIATED BY NICKEL(II) COMPLEX IN ENVIRONMENTALLY FRIENDLY MEDIUM

E. Duñach[a], M. J. Medeiros[b*]

[a] *Laboratoire de Chimie Bioorganique, , Université de Nice-Sophia Antipolis, CNRS, UMR 6001, Institut de Chimie de Nice, Parc Valrose, 06108 Nice Cedex 2, France*

[b]*Centro de Química, Universidade do Minho, Largo do Paço,* 4704-553 *Braga, Portugal*



Ni(II)-catalysed radical-type cyclization of unsaturated bromoethers to the corresponding cyclic compounds in EtOH and EtOH-H_2O mixures.

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[a] *Laboratoire de Chimie Bioorganique, , Université de Nice-Sophia Antipolis, CNRS, UMR 6001, Institut de Chimie de Nice, Parc Valrose, 06108 Nice Cedex 2, France*

[b]*Centro de Química, Universidade do Minho, Largo do Paço,* 4704-553 *Braga, Portugal*

Abstract: An improved procedure has been developed using a catalytic amount of a nickel(II) complex in the efficient and selective electrochemical cyclization of propargyloxy and allyloxy bromo derivatives into substituted tetrahydrofurans using ethanol and ethanol-water mixtures as environmentally friendly systems. The reduction of the substrates proceeded via one-electron cleavage of the carbon-bromine bond to form a radical-type intermediate that undergoes cyclization to afford the tetrahydrofuran structures in good yields.

Keywords: ethanol solvent, cyclization, nickel(II) complex, electroreduction, heterocycles.

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* Corresponding author: Tel.: +351 253 604050; Fax: +351 253 678983

E-mail address: medeiros@quimica.uminho.pt (M.J. Medeiros)

1. Introduction

The synthesis of substituted tetrahydrofurans constitutes an important and attractive subject in organic synthesis. Indeed, the furofuran moiety is an important subunit in a wide range of biologically active natural compounds [1,2] and this structural unit is found in antibiotics, diuretics, analgesics, anti-rheumatic and anti-tumor agents. They are also used as perfuming or flavouring ingredients in foodstuffs [3-5].

Intramolecular cyclization by trapping of a radical intermediate with an internal π-bond system is a promising strategy for the construction of carbocyclic and heterocyclic molecules under mild conditions [6-8]. Reported radical methods generally utilizing SmI_2 or organotin reagents as radical generators need stoichiometric amounts and may be troublesome in the purification of the products [7]. However, these drawbacks have stimulated the interest in developing novel and environmentally-friendly reagents and procedures for the generation of radical species. In addition to other synthetic methods, the electrochemical nickel-catalyzed radical-type cyclizations for the construction of heteroring systems has been shown to be a convenient alternative for the synthesis of cyclic compounds. This alternative has been reported in the case of the reductive cyclization involving various organic halides [9-11], bromoacetals possessing electron-deficient olefinic moieties [12], 2-haloaryl ethers containing unsaturated side-chains [13] and α-bromopropargyl esters and ethers [14-18].

In general, all these reported indirect electrochemical cyclizations use *N*,*N*-dimethylformamide (DMF) or acetonitrile (ACN) as the solvents, which may present some toxicity [19,20].

In order to combine both a cleaner synthesis using a catalytic amount of a mediator and a non-pollutant solvent, in a previous investigation we undertook a preliminary study on the electroreduction of compounds **2a-c** in ethanol and ethanol-water mixtures as the solvents using constant-current electrolyses [21]. Following this approach, in this work we present a detailed study on the catalytic reduction of starting unsaturated halides **1** and **2** by electrogenerated nickel(I) complexes in protic solvents using cyclic voltammetry and

controlled-potential electrolyses. Apart from being environmentally less aggressive, this electrochemical procedure in alcohol solvents makes the purification of the products much easier.

2. Experimental part

2.1. Reagents

Each of the following chemicals was used as received: nickel(II) bromide (Aldrich, 98%), 1,4,8,11-tetramethyl-1,4,8,11-tetraazacyclotetradecane (tetramethylcyclam, tmc, Fluka, 97%). Ethanol (EtOH) from Riedel-de-Häen, Analytical Reagent, was used as received. We purchased tetraethylammonium bromide (TEABr) with a purity of 98% from Fluka; this electrolyte was stored in a vacuum oven at 80ºC to remove traces of water. Deaeration procedures were carried out with zero-grade argon (Air Products). Published procedures were employed for the preparation of [Ni(tmc)]Br_2 [22] and of [1-bromo-2-methoxy-2-(prop-2'-ynyloxy)ethyl]benzene (**1a**) [23], 1-[2-bromo-2-phenyl-1-(prop-2'-ynyloxy)ethyl]-4-methoxybenzene (**1b**) [23], ethyl 2-bromo-3-(3′,4′-dimethoxyphenyl)-3-propargyloxy-propanoate (**2a**) [23], ethyl 2-bromo-3-(3′,4′-methylene-dioxophenyl)-3-(propargyloxy)propanoate (**2b**) [23] and ethyl 2-bromo-3-(3′,4′-dimethoxyphenyl)-3-(allyloxy)propanoate (**2c**) [23].

Synthesis of 2-methoxy-4-methylene-3-phenyltetrahydrofuran (**3**) and 2-(4'-methoxyphenyl)-4-methylene-3-phenyltetrahydrofuran (**4**), 2-(3′,4′-dimethoxyphenyl-3-ethoxycarbonyl-4-methylene-tetrahydrofuran (**5**), 2-(3′,4′-dimethoxyphenyl-3-ethoxycarbonyl-4-methyl-2,5-dihydrofuran (**6**), 2-(3′,4′-methylenedioxophenyl)-3-ethoxycarbonyl-4-methylenetetrahydrofuran (**7**), 2-(3′,4′-methylenedioxophenyl)-3-ethoxycarbonyl-4-methyl-2,5-dihydrofuran (**8**), and 2-(3′,4′-dimethoxyphenyl)-3-ethoxycarbonyl-4-methyltetrahydrofuran (**9**) was based on the method published by McCague *et al*.[24]. We identified the compounds

by means of ^{1}H NMR spectrometry with a Varian Unity Plus 300-MHz instrument ($CDCl_3$): (a) for **3**, δ 3.41 (3H, s, OCH_3); 3.81 (1H, broad s, 3-H); 4.61 (2H, app q, J 2.0, 5-H_2); 4.99 (1H, app q, J 2.0, C=CHH); 5.02 (1H, broad s, 2-H); 5.12 (1H, app q, J 2.0, C=CHH); 7.20-7.40 (5H, m , C_6H_5) ppm; (b) for **4**, δ 3.64-3.70 (1H, m, 3-H); 3.78 (3H, s, OCH_3); 4.66 (1H, dq, J 13.2 and 2.4, 5-H_a); 4.72 (1H, app q, J 2.4, C=CHH); 4.79 (1H, d, J 9.3, 2-H); 4.84 (1H, broad d, J 13.2, 5-H_b); 5.09 (1H, app q, J 2.1, C=CHH); 6.81 (2H, app d, J 8.5, 2'-H and 6'-H); 7.14 (2H, app d, J 8.5, 3'-H and 5'-H); 7.22-7.34 (5H, m, Ph) ppm; (c) for **5**, δ 1.28 (3H, t, *J* = 7.0 Hz), 3.49 (1H, apparent ddd, *J* = 8.7, 2.4, 2.4 Hz), 3.88 (3H, s), 3.90 (3H, s), 4.22 (2H, qABq, *J* = 7.0, 18.0 Hz), 4.50 (1H, apparent dq, *J* = 13.2, 2.4 Hz), 4.65 (1H, broad apparent d, *J* = 13.2 Hz), 5.11 (1H, apparent q, *J* = 2.4 Hz), 5.19 (1H, d, *J* = 8.7 Hz), 5.20 (1H, apparent q, *J* = 2.4 Hz), 6.84 (1H, d, *J* = 8.7 Hz), 6.91–6.96 (2H, m); (d) for **6**, δ □1.15 (3H, t, *J* = 7.0 Hz), 2.19 (3H, d, *J* = 1.2 Hz), 3.87 (3H, s), 3.88 (3H, s), 4.08 (2H, qABq, *J* = 7.0, 11.0 Hz), 4.72 (1H, apparent ddd, *J* = 1.2, 3.6, 15.0 Hz), 4.89 (1H, apparent ddd, *J* = 0.9, 5.7, 15.0 Hz), 5.90 (1H, m), 6.83 (1H, d, *J* = 8.1 Hz), 6.84 (1H, broad s), 6.88 (1H, dd, *J* = 8.1, 1.8 Hz); (e) for **7**, δ 1.28 (t, *J* = 7.2 Hz, 3 H, $OCH_2C\mathit{H}_3$), 3.42–3.47 (m, 1 H, 3-H), 4.21 (qABq, *J* = 11.0, 7.2 Hz, 2 H, $OC\mathit{H}_2CH_3$), 4.49 (apparent dq, *J* = 13.0, 2.4 Hz, 1 H, 5-H), 4.63 (br apparent d, *J* = 13.0 Hz, 1 H, 5-H), 5.10 (apparent q, *J* = 2.4 Hz, 1 H, =CH), 5.15 (d, *J* = 8.7 Hz, 1 H, 2-H), 5.18 (apparent q, *J* = 2.4 Hz, 1 H, =CH), 5.96 (s, 2 H, OCH_2O), 6.77 (d, *J* = 8.0 Hz, 1 H, 5′-H), 6.88 (dd, *J* = 8.0, 1.8 Hz, 1 H, 6′-H), 6.90 (d, *J* = 1.8 Hz, 1 H, 2′-H); (f) for **8**,□ δ 1.16 (t, *J* = 7.2 Hz, 3 H, $OCH_2C\mathit{H}_3$), 2.18 (apparent d, *J* = 1.2 Hz, 3 H, 4-CH_3), 4.09 (qABq, *J* = 10.8, 7.2 Hz, 2 H, $OC\mathit{H}_2CH_3$), 4.71 (apparent ddd, *J* = 15.0, 3.5, 1.0 Hz, 1 H, 5-H), 4.87 (apparent ddd, *J* = 15.0, 5.0, 1.0 Hz, 1 H, 5-H), 5.83–5.87 (m, 1 H, 2-H), 5.94 (s, 2 H, OCH_2O), 6.76 (d, *J* = 8.0 Hz, 1 H, 5′-H), 6.77 (d, *J* = 1.8 Hz, 1 H, 2′-H), 6.82 (dd, *J* = 8.0, 1.8 Hz, 1 H, 6′-H); and (g) for **9**, δ 1.07 (d, *J* = 6.9 Hz, 2.55 H, 4-CH_3), 1.18 (d, *J* = 6.6 Hz, 0.45 H, 4-CH_3), 1.25 (t, *J* = 7.0 Hz, 0.45 H, $OCH_2C\mathit{H}_3$), 1.28 (t, *J* = 7.2 Hz, 2.55 H, $OCH_2C\mathit{H}_3$), 2.55 (apparent t, *J* = 9.0, 8.7 Hz, 0.15 H, 3-H), 2.70–2.85 (m, 1 H, 4-H), 3.00 (apparent dd, *J* = 9.0, 7.8 Hz, 0.85 H, 3-H), 3.66 (apparent dd, *J* = 8.7, 6.6 Hz, 1 H, 5-H_a), 3.87 (3H, s, OCH_3), 3.89 (s, 3 H, OCH_3), 4.12–4.24 (m, 2 H, $OC\mathit{H}_2CH_3$), 4.28 (dd, *J* = 8.4

and 6.6 Hz, 1 H, 5-H_b), 5.05 (d, *J* = 9.0 Hz, 0.15 H, 2-H), 5.19 (d, *J* = 7.8 Hz, 0.85 H, 2-H), 6.83 (d, *J* = 9.0 Hz, 1 H, 5′-H), 6.88–6.92 (m, 2 H, 2′-H and 6′-H). These compounds were utilized as standards for the determination of gas chromatographic response factors.

2.2. Cells and electrodes

Cyclic voltammograms were recorded in a three-electrode, two-compartment cell as described in earlier publications [25]. The working electrodes were fabricated from 3-mm-diameter glassy carbon rods (Tokai Electrode Manufacturing Company, Tokyo, Japan, Grade GC-20) press-fitted into Teflon shrouds to provide planar, circular working electrodes with areas of 0.07 cm^2. Before use, the electrodes were cleaned with an aqueous suspension of 0.05-µm alumina (Buehler) on a Master-Tex (Buehler) polishing pad. The counter electrode was a Pt spiral in the same compartment. The experimental reference electrode was a Ag / AgCl / 3 mol dm^{-3} KCl in water, separated from the working electrode by a sinter and Luggin capillary. All solutions were deoxygenated with a fast stream of argon before each experiment. For controlled-potential electrolysis and product analysis, a divided cell with an anodic and a cathodic compartment separated by a glass sinter (as have been described in earlier publications [26]) was used. Working electrodes for controlled-potential electrolyses were disks (0.2 cm in thickness, 2.4 cm in diameter, and approximately 100 cm^2 in total area) sliced from reticulated vitreous carbon logs (RVC 2X1-100S, Energy Research and Generation, Oakland, CA) while a carbon rod was the counter electrode. Procedures for cleaning and handling of these electrodes have been described previously [27]. The catholyte and anolyte compartments were each 15 cm^3 and the reference electrode was again Ag / AgCl / 3 mol dm^{-3} KCl in water mounted in a Luggin capillary. All preparative electrolyses were carried out in an atmosphere of argon, owing to the extreme sensitivity of Ni(I) complexes to oxygen [28], and the catholyte solutions were stirred with a magnetic bar.

All potentials are quoted with respect to Ag / AgCl / 3 M KCl in water reference electrode (–0.036 *vs* SCE).

2.3. Instrumentation

Cyclic voltammograms were obtained and controlled-potential electrolyses were carried out with the aid of an AUTOLAB model PGSTAT12 potentiostat–galvanostat. The data from the above experiments were acquired and stored by GPES 4.9 software, which controlled a data acquisition board installed in a personal computer.

2.4. Identification and quantification of products

Gas chromatographic analyses were accomplished with the aid of a Chrompack, type CP 9000, instrument equipped with flame ionization detector. Products were separated with a 25 m x 0.25 mm i.d. capillary column (WCOT fused silica) with a stationary phase of poly(methylphenylsiloxane). A known quantity of an electroinactive internal standard (*n*-hexadecane and *n*-tetradecane) was added to a solution before each experiment to allow quantitative determination of the electrolysis products. Gas chromatographic response factors were measured experimentally with authentic samples of each product, and all product yields tabulated in this paper represent the absolute percentage of starting material incorporated into a particular product. In order to isolate the products, the ethanol solvent was evaporated under vacuum, the reaction mixture hydrolysed with 0.1M HCl saturated with NaCl, up to pH 1-2, extracted with CH_2Cl_2 and washed with H_2O. The dried ($MgSO_4$) organic layer was evaporated. The crude residue was submitted to flash chromatography over silica gel (230-400 mesh) using diethyl ether-light petroleum 1:2 (for **3**), diethyl ether-light petroleum 1:3 (for **4**) and ethyl acetate-light petroleum mixtures (**5** – **9**) as eluents.

Identitification of the electrolysis products was confirmed by means of a Hewlett-Packard 5890 Series II gas chromatograph coupled to a Hewlett-Packard 5971 mass-selective detector: (a) for **3,** *m/z* (70 eV) 290, M^+ (0.5); 159, $[M\text{-}CH_3O]^+$ (8); 129, $[M\text{-}CH_3OCHOH]^+$

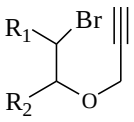
(100); 91, $[C_6H_5CH_2]^+$ (32); 77, $[M\text{-}C_6H_5]^+$ (11); (b) for **4**, *m/z* (70 eV) 266, M^+ (10); 129, $[M\text{-}CH_3OC_6H_4CHOH]^+$ (100); 91, $[C_6H_5CH_2]^+$ (8); 77, $[C_6H_5]^+$ (18); (c) for **5**, *m/z* (70 eV) 292, M^+ (23); 277, $[M - CH_3]^+$ (0.6); 218, $[M - CO_2C_2H_5 - H]^+$ (6); 165, $[(CH_3O)_2C_6H_3CO]^+$ (19); 126, $[H_5C_2O_2CC_4H_5]^+$ (51); 98, $[C_5H_6O_2]^+$ (100); (d) for **6**, *m/z* (70 eV) 292, M^+ (100); 277, $[M - CH_3]^+$ (16); 263, $[M - C_2H_5]^+$ (25); 215, $[M - C_2H_5O - CH_3OH]^+$ (49); 165, $[(CH_3O)_2C_6H_3CO]^+$ (66); 77, $[C_6H_5]^+$ (20); 29, $[COH]^+$ (44); (e) for **7**, *m/z* (70 eV) 276, M^+ (35); 247, $[M - C_2H_5]^+$ (3); 202, $[M - CO_2C_2H_5 - H]^+$ (18); 149, $[CH_2O_2C_6H_3CO]^+$ (45); 126, $[H_5C_2O_2CC_4H_5]^+$ (59); 98, $[C_5H_6O_2]^+$ (100); (f) for **8**, *m/z* (70 eV) 276, M^+ (100); 261, $[M - CH_3]^+$ (17); 247, $[M - C_2H_5]^+$ (34); 202, $[M - CO_2C_2H_5 - H]^+$ (82); 149, $[CH_2O_2C_6H_3CO]^+$ (64); 77, $[C_6H_5]^+$ (7); 29, $[COH]^+$ (22) and (g) for **9**, *m/z* (70 eV) 294, M^+ (84); 279, $[M - CH_3]^+$ (26); 265, $[M - C_2H_5]^+$ (69); 220, $[M - CO_2C_2H_5 - H]^+$ (10); 205, $[M - CO_2C_2H_5 - CH_3 - H]^+$ (35); 165, $[(CH_3O)_2C_6H_3CO]^+$ (100); 29, $[COH]^+$ (16). These identifications were checked by comparison with analytical data of authentic samples.

3. Results and discussion

3.1. The electrochemistry of bromo derivatives 1 and 2

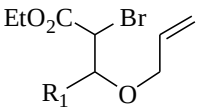
The electrochemical study of 2 mM solutions of **1** and **2** in ethanol containing 0.10 M Et_4NBr as the supporting electrolyte at a vitreous carbon electrode was performed by cyclic voltammetry. It was observed that both the propargyl 2-bromoethers **1a** and **1b** showed a first irreversible reduction wave at potentials near to –1.53 and –1.62 V *vs* Ag/AgCl, respectively, corresponding to the reductive cleavage of the carbon-bromine bond. Figure 1 (curve A)

indicates the cyclic voltammogram recorded at a scan rate of 200 mV s^{-1} for the direct reduction of **1a**.

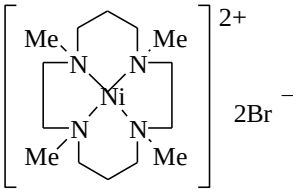


1a: R_1 = phenyl; R_2 = 4-methoxy
b: R_1 = phenyl; R_2 = 4-methoxyphenyl

2a: R_1= ethoxycarbonyl; R_2 = 3,4-dimethoxyphenyl
b: R_1= ethoxycarbonyl; R_2 = 3,4-methylenedioxophenyl



2c: R_1 = 3,4-dimethoxyphenyl



$Ni(tmc)Br_2$

For propargyloxy and allyloxy bromoesters **2a**, **2b** and **2c** in ethanol solution, a first irreversible reduction peak was observed at potentials of approximately –1.54, –1.50 and –1.45 V *vs* Ag/AgCl, respectively, followed by a second irreversible reduction peak at more negative potentials, as shown in Figure 2, curve A, for **2a**. The first irreversible reduction wave was also attributed to the cleavage of the carbon-bromine bond. Similar results were found in cyclic voltammetry run in ethanol / water mixtures.

3.2. The electrochemistry of $[Ni(tmc)]Br_2$ in the absence and in the presence of bromoalkoxylated compounds 1 and 2

Cyclic voltammetric studies of solutions of the nickel(II) complex, $[Ni(tmc)]Br_2$, in EtOH / Et_4NBr (0.1M) have been carried out, as shown as curve B, Figure 1, recorded at 200 mVs^{-1}. A one-electron reversible $[Ni(tmc)]^{2+}$ to $[Ni(tmc)]^{+}$ reduction peak is observed, for which the cathodic peak potential (Epc) appeared at -0.91 V and the anodic peak potential

(Epa) at -0.80 V. The ratio of the peak currents (I_{pa}/I_{pc}) was close to unity. Formal electrode potential is –0.86 V *vs* Ag/AgCl. These observations are in agreement with the results of earlier investigations carried out in DMF as the solvent [14-18].

Controlled-potential electrolyses were also carried out at potentials just beyond the reduction peaks for solutions of the Ni(II) complex in ethanol media. In all cases *n* values close to one electron per molecule were obtained. Hence, all these data indicated that the electrode reaction in EtOH solutions is:

$$[Ni(tmc)]^{2+} + e^- \rightleftharpoons [Ni(tmc)]^{+}$$

in agreement with literature data on other non-protic solvents [28-31].

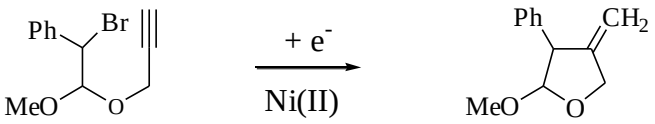
The reduction of $[Ni(tmc)]Br_2$ in the presence of substrates **1a-b** and **2a-c** has been carried out. In all cases, the experiments by cyclic voltammetry indicated that the addition of bromoalkoxylated compounds to the Ni(II) solutions resulted in an important increase of the reduction peak intensity at the reduction potential of the mediator as well as in the disappearance of the anodic wave as a result of the catalyst-substrate reaction. For example, Figures 1 and 2 (curves C and D) present the cyclic voltammograms recorded for solutions of 1.0 mM of $[Ni(tmc)]Br_2$ in the presence of increasing concentrations of **1a** and **2a**, respectively. A positive shift in the cathodic peak potential with an increase in the cathodic peak current for the reduction of $[Ni(tmc)]^{2+}$ was observed, as it was recycled catalytically. A cathodic post-wave can also be observed at more negative potentials (Figures 1 and 2, curve C), that we believe arises from the formation of $[Ni(tmc)]^{+}$ complex unable to locate a molecule of unsaturated halide close to the electrode surface due to its depletion. For higher substrate concentrations, all the $[Ni(tmc)]^{+}$ formed reacted with the unsaturated halide close to the surface so that the cathodic post-wave was no longer observed. All these same trends were also observed for substrates **1b**, **2b** and **2c**.

The data from the voltammetric experiments for **1a-b** and **2a-c** are presented in Table 1. It can be seen that the extent of the catalytic reaction increases with increasing the concentration of the substrates for a given mediator concentration. Moreover, the rates of the catalytic cycles are high enough to enable the electrolyses of compounds **1** and **2** in the

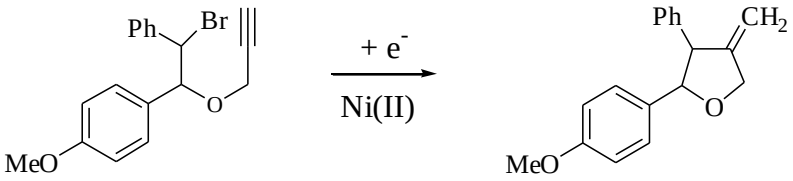
presence of $[Ni(tmc)]^{2+}$ to occur at current densities acceptable for efficient electrosyntheses. These observations lead us to conclude that the reduction of **1a-b** and **2a-c** by the electrogenerated nickel(I) complex in EtOH and EtOH/H_2O is a fast catalytic process. The results are also consistent with previously reported investigations in DMF as the solvents [15,17,18].

Preparative controlled-potential electrolyses were performed at reticulated vitreous carbon electrodes in EtOH and EtOH/H_2O mixtures containing 0.1 M TEABr, $[Ni(tmc)]Br_2$ and **1** or **2** at − 0.90 V *vs* Ag/AgCl/ 3M aqueous KCl. Experimental parameters, such as the ratio of substrate to catalyst and the influence of water were examined to evaluate their effect on the product yields. Compiled in Tables 2 and 3 are the coulometric *n* values (based on the consumption of substrates) and product yields obtained from these experiments; each entry represents the average of two or three separate runs. Coulometric *n* values close to unity indicated that the $[Ni(tmc)]^+$-catalysed reaction with **1** and **2** involves a one-electron reductive cleavage of the carbon-halogen bond to afford a radical intermediate. None of the starting material remained unreduced and, within experimental error, the total yield of the recovered products was almost quantitative.

As illustrated in entries 1-3 and 7-9 of Table 2, the catalytic reduction of **1a-b** by electrogenerated $[Ni(tmc)]^+$ in EtOH led to the formation of the expected heterocyclic products, namely 2-methoxy-4-methylene-3-phenyl-tetrahydrofuran (**3**) (Eq. 1) and 2-(4'-methoxyphenyl)-4-methylene-3-phenyl-tetrahydrofuran (**4**) (Eq. 2), which were obtained in yields ranging from 95 to 98%. The product yields were not sensitive to the [RBr]/[Ni(II)] ratio. It is worth noting that a catalytic amount of 5 mol% of Ni(II) catalyst with respect to the substrate still afforded an efficient cyclization.



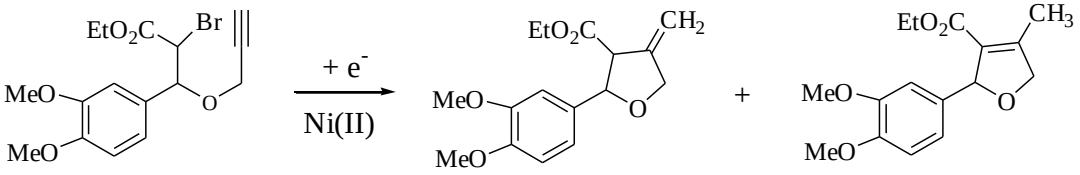
1a **3** (Eq.1)



1b **4** (Eq. 2)

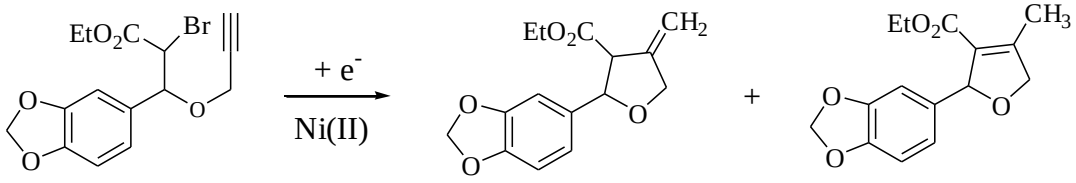
To test the effect of the presence of water in the systems, electrolyses of **1a-b** in EtOH/H_2O (9:1) were performed (Table 2, entries 4-6 and 10-12). It can be observed that the presence of water did not exert any major effect neither on the yield of the products **3** and **4** nor on the coulometric *n* value.

These studies were extended to bromoester derivatives **2a-c**. Hence, as shown in entries 1-2, 6-7 and 11-12 in Table 3, the catalytic reduction of substrates **2a-c** in EtOH gave rise in each case to two major products; 2-(3′,4′-dimethoxyphenyl-3-ethoxycarbonyl-4-methylene-tetrahydrofuran (**5**) and 2-(3′,4′-dimethoxyphenyl-3-ethoxycarbonyl-4-methyl-2,5-dihydrofuran (**6**) from **2a** (Eq. 3):



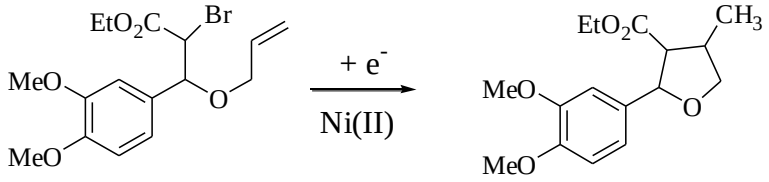
2a **5** **6** (Eq. 3)

2-(3′,4′-methylenedioxophenyl)-3-ethoxycarbonyl-4-methylenetetrahydrofuran (**7**) and 2-(3′,4′- methylenedioxophenyl)-3-ethoxycarbonyl-4-methyl-2,5-dihydrofuran (**8**) from **2b** (Eq. 4):



2b **7** **8** (Eq. 4)

and two diastereoisomers of 2-(3′,4′-dimethoxyphenyl-3-ethoxycarbonyl-4-methyltetrahydrofuran (**9**) from **2c** (Eq. 5):



2c **9** (Eq. 5)

As presented in Table 3, the product yields and the coulometric *n* values were here again not sensitive to changes in the initial ratios of $[Ni(tmc)]^{2+}$ and **2**.

The influence of added water on the reaction selectivity with α-bromoesters **2a-c** was also investigated. Hence, when EtOH/H_2O (9:1) was used as the solvent (Table 3, entries 3-5, 8-10 and 13-14), the electrolyses afforded the corresponding expected cyclised products with no significant change in the product yields. Again, changes on the ratio [RBr] / [Ni(II)] did not interfere in the reaction outcome.

The data obtained suggests in these protic solvents a single-electron mechanism (Scheme 1). Thus, after the one-electron reduction of $[Ni(tmc)]^{2+}$ to form $[Ni(tmc)]^{+}$, the later transfers one electron to the bromoalkoxylated substrates with cleavage of the carbon-bromine

bond. The radical-type intermediates undergo an intramolecular cyclization on the side-chain unsaturation to afford a halide anion and a radical intermediate such as **11** and **13**, regenerating the starting $[Ni(tmc)]^{2+}$ species. The cyclised radicals **11** and **13** can abstract an hydrogen atom from the medium (either from the solvent [32-35] or from the tetralakylammonium cations of the supporting electrolyte [36]) to give the corresponding tetrahydrofuran derivatives **3**, **4**, **5**, **7** and **9** in good yields, as proposed for reactions (2) and (3) in Scheme 1, for propargylic and allylic ethers, respectively. In addition, there is evidence in the literature that EtOH can act as an hydrogen-atom donor [32-35] and the EtOH radical formed can preferentially recombine by dimerisation or can be reduced at much more negative potentials, approximately, −1.25 V *vs* SHE [32-35]. In this case the electron stoichiometry should correspond to one Ni(I) species per unsaturated halide.

At the outset of this work, an important goal was to optimize the preparation of tetrahydrofuran derivatives **3**-**9** by indirect electrochemical reduction of **1** and **2**. The results of the present study involve a more selective radical-type activation and reactivity of the carbon–halogen bond of the substrates, and enable a more selective formation of expected tetrahydrofuran derivatives **3**-**9**, as compared to the results obtained in earlier investigations, run at constant current in one-compartment cell with sacrificial zinc or magnesium anodes [21]. The experimental conditions of the present work, such as, the technique used, the cell design, the nature of the electrodes and of the supporting electrolyte differ significantly from earlier work.

4. Conclusion

The results of the cyclizations of bromobenzyl derivatives **1a-b** and α-bromoester derivatives **2a-c** in EtOH and EtOH/H_2O mixtures as the solvents are in agreement with previous results reported by Medeiros *et al*. [15,17,18] in DMF, where the intramolecular cyclization of unsaturated bromoethers led to the corresponding cyclic compounds.

In summary, our results have established that the cyclization can be carried out under mild conditions in ethanol or in a mixture of ethanol/water as solvents. The process can also be accomplished at room temperature using a catalytic amount of Ni(II) complex in an environmentally friendly procedure. Moreover, the use, removal and disposal of toxic *n*-tributyltin hydride as the classical radical source (and its by-products) are avoided.

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CAPTION FOR FIGURES

Figure 1. Cyclic voltammograms recorded with a glassy carbon electrode (area = 0.07 cm^2) at 200 mV s^{-1} in EtOH containing 0.10 M TEABr: (A) 2 mM **1a**; (B) 1 mM [Ni(tmc)]Br_2; (C) 1 mM [Ni(tmc)]Br_2 and 2 mM **1a**; (D) 1 mM [Ni(tmc)]Br_2 and 10 mM **1a.**

Figure 2. Cyclic voltammograms recorded with a glassy carbon electrode (area = 0.07 cm^2) at 100 mV s^{-1} in EtOH containing 0.10 M TEABr: (A) 2 mM **2a**; (B) 1 mM [Ni(tmc)]Br_2; (C) 1 mM [Ni(tmc)]Br_2 and 2 mM **2a**; (D) 1 mM [Ni(tmc)]Br_2 and 10 mM **2a.**

Table 1. Peak-Current Ratios Obtained from Cyclic Voltammograms of Solutions of EtOH Containing 0.10 M TEABr, 1.0 mM $[Ni(tmc)]^{2+}$ and Various Concentrations of 1 and 2 at 100 mV s^{-1}

Compound	I_c/I_d[a]		
	$\gamma = 2$[b]	$\gamma = 5$[b]	$\gamma = 10$[b]
1a	2.2	5.5	10.4
1b	2.7	6.2	10.0
2a	2.2	5.1	9.8
2b	3.2	5.1	7.9
2c	2.1	4.8	9.9

[a] Ic - catalytic peak current intensity of the catalyst in the presence of substrate and Id - peak current intensity of the catalyst in the absence of substrate; [b] γ = [RBr] / [Ni (II)].

Table 2. Coulometric Data and Product Yields for Catalytic Reduction of 1a and 1b by [Ni(tmc)]$^+$ Electrogenerated at Reticulated Vitreous Carbon Cathodes in EtOH Containing 0.10 M TEABr. E_p = – 0.90 V *vs* Ag/AgCl.

Entry	[Ni(tmc)]$^{2+}$, mM	[RBr], mM	n[a]	Product yield, %
RBr = [1-bromo-2-methoxy-2-(prop-2'-ynyloxy) ethyl] benzene (**1a**)				**3**
2	0.4	2.1	1.0	96
3	0.3	2.5	1.0	99
4	0.1	2.6	0.9	98
5[b]	0.4	2.1	1.0	88
6[b]	0.3	2.8	0.9	94
7[b]	0.1	2.7	0.9	94
RBr = 1-[2-bromo-2-phenyl-1-(prop-2'-ynyloxy)ethyl]-4-methoxybenzene (**1b**)				**4**
8	0.4	2.1	0.9	96
9	0.3	2.7	1.0	79
10	0.1	2.7	0.9	95
11[b]	0.4	2.0	1.0	93
12[b]	0.3	2.5	0.9	100
13[b]	0.1	2.7	1.0	100

[a] Number of electrons per molecule of starting material. [b] Carried out in EtOH / H_2O (9:1)

Table 3. Coulometric Data and Product Yields for Catalytic Reduction of 2a, 2b, and 2c by $[Ni(tmc)]^+$ Electrogenerated at Reticulated Vitreous Carbon Cathodes in EtOH Containing 0.10 M TEABr. E_p = – 0.90 V *vs* Ag/AgCl.

Entry	$[Ni(tmc)]^{2+}$, mM	[**2**], mM	n[a]	Products Yield %	
RBr = ethyl 2-bromo-3-(3′,4′-dimethoxyphenyl)-3-propargyloxy-propanoate (**2a**)				**5**	**6**
1	0.4	2.0	1.1	86	14
2	0.3	2.6	1.0	92	7
3[b]	0.4	1.9	1.0	90	10
4[b]	0.2	2.5	1.0	86	11
5[b]	0.1	2.6	0.9	77	23
RBr = ethyl 2-bromo-3-(3′,4′-methylenedioxophenyl)-3-(propargyloxy)propanoate (**2b**)				**7**	**8**
6	1.1	1.9	1.0	90	6
7	0.4	2.4	1.0	83	17
8[b]	0.4	2.1	0.9	94	6
9[b]	0.3	2.9	1.0	86	14
10[b]	0.3	2.9	1.0	61	24
RBr = ethyl 2-bromo-3-(3′,4′-dimethoxyphenyl)-3-(allyloxy)propanoate (**2c**)				**9** (d.r.)[c]	
11	0.4	2.0	1.0	47 (91:9)	
12	0.3	3.0	1.0	53 (95:5)	
13[b]	0.4	2.0	1.0	86 (94:6)	
14[b]	0.3	2.9	1.0	82 (94:6)	

[a] Number of electrons per molecule of starting material. [b] Carried out in EtOH / H_2O (9:1). [c] Diastereomeric (*cis*-to-*trans*) ratio as determined by GC.

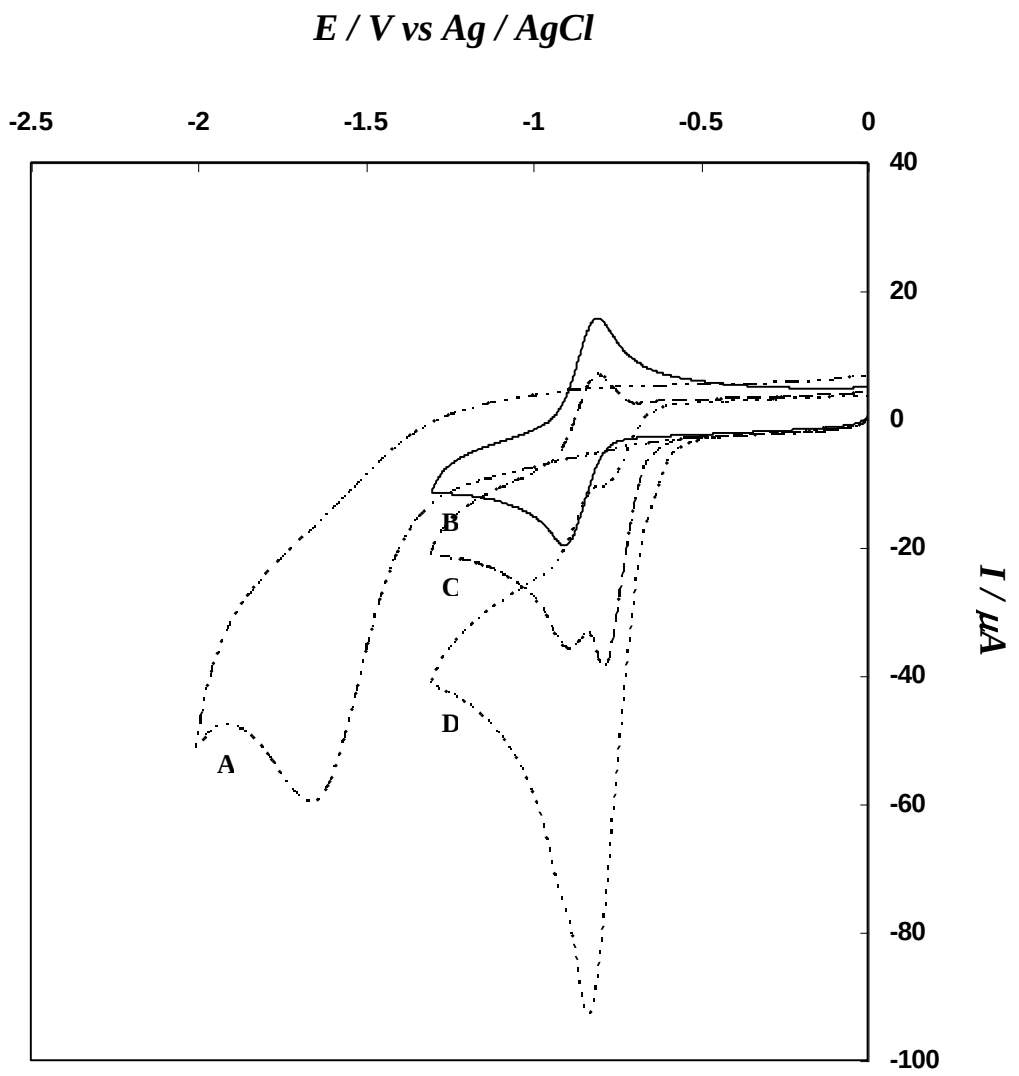


Figure 1

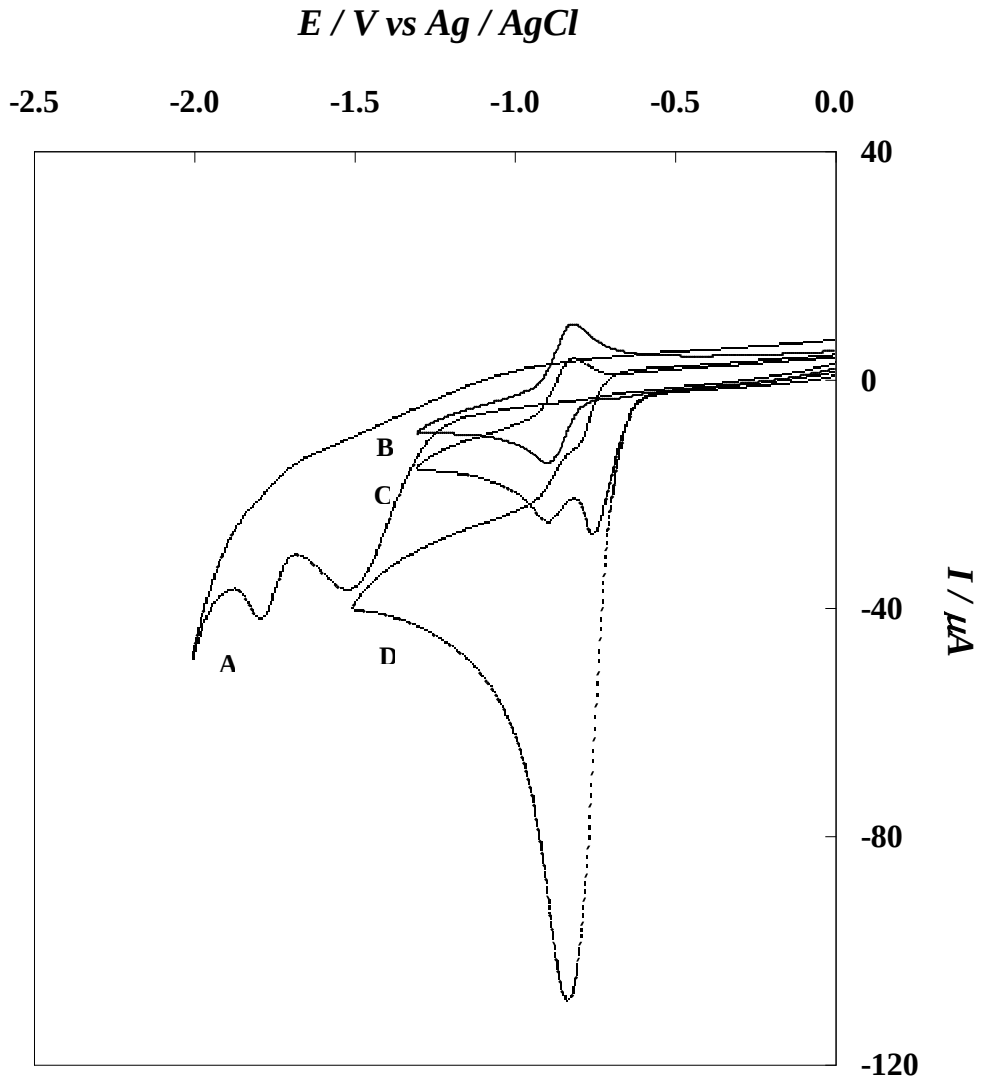
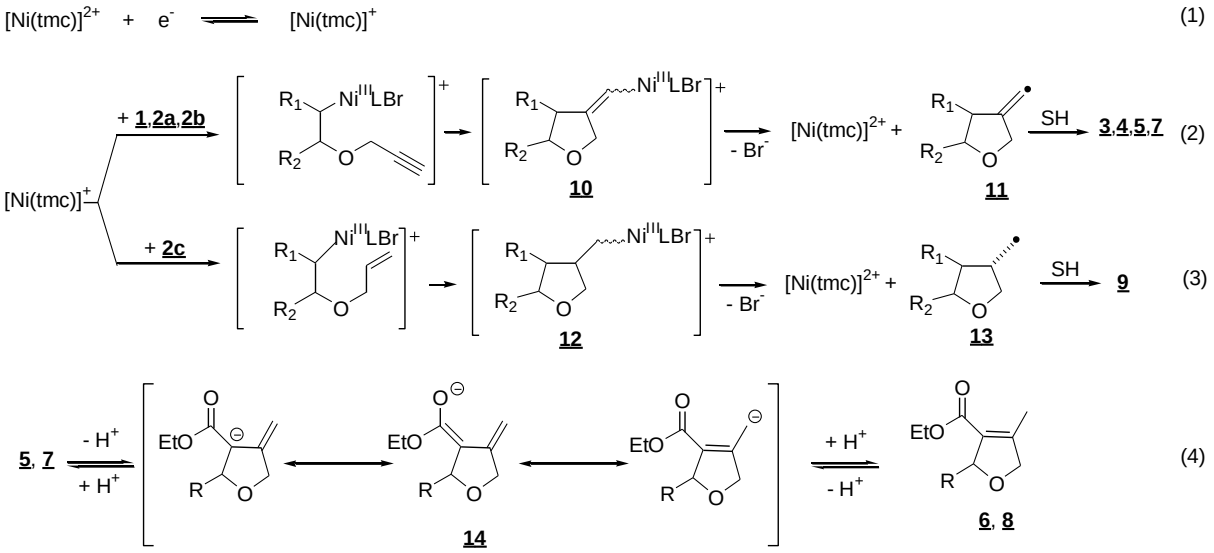


Figure 2


[Ni(tmc)]2+ + e- [Ni(tmc)]+ (1)
+ 1,2a,2b
[Ni(tmc)]+
R1 NiIIILBr R2 O
10
- Br-
[Ni(tmc)]2+ +
11
SH
3,4,5,7 (2)
+ 2c
12
13
9 (3)
5, 7
- H+
+ H+
EtO
R
O
14
+ H+
- H+
6, 8 (4)

Scheme 1